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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,477	04/13/2001	Anthony A. Fossa	PC10148AGPR	2582

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,477	FOSSA, ANTHONY A.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16 and 18-35* is/are pending in the application.

4a) Of the above claim(s) *1-3,5-12,23-29,32,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,13,14,16,18-22,30,31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 10/20/03, claims 4, 13, 14, 16, 18, 33 have been amended, and claims 15 and 17 cancelled. Claims 1-14, 16, 18-35 remain pending.

Applicants' election of Group 7 is acknowledged. Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are examined in this Office action; claims 1-3, 5-12, 23-29, 32, 34, 35 are withdrawn from consideration.

The following abbreviations are used herein:

"**CRFA**" = corticotropin releasing factor antagonist

"**GHS**" = growth hormone secretagogue

"**GH**" = growth hormone

"**ES-1**" = the first elected specie, i.e., the following:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine

"**ES-2**" = the second elected specie, i.e., the following:

2-Amino-N-[1-benzyloxymethyl-2-(2,3a-dimethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo [4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and

process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

One may discern two categories of embodiment: (a) those compositions in which growth hormone is present, and (b) those compositions in which growth hormone is not present. This ground of rejection targets the latter.

The instant claims require that the CRFA be one of those that is recited in claim 4. However, it remains to be determined whether any of the compounds (recited in claim 4) are in fact antagonists of corticotropin releasing factor receptors. It is stated p. 69, lines 23-30 (specification) that one can determine the propensity of compounds to bind to a CRF receptor. No doubt the biochemist of ordinary skill could carry out assays to determine whether or not a compound will bind to a CRF receptor. However, the fact that an assay can be conducted does not mean that any particular result will be obtained. As it happens, where receptor activation and inhibition is concerned, structure/activity relationships are unpredictable. Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith, "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity

- Keri, Gy ["Structure-activity relationship studies of novel somatostatin analogs with antitumor activity" *Peptide Research* (1993), 6(5), 281-8] discloses (table 4)

an example of a peptide which inhibits GH release in vitro, but fails to inhibit GH release in vivo.

- Tolle, V (*Neuroendocrinology* **73** (1) 54-61, 2001) discloses that certain analogs of ghrelin fail to stimulate GH release.

- Rigamonti (*Alcohol* **20** (3) 293-304, 2000) discloses that *gamma*-hydroxybutyric acid and baclofen both fail to stimulate GH release.

- Pinilla L (*Hormone Research* **51** (5) 242-7, 1999) discloses that 8-Br-cGMP was ineffective in eliciting GH release.

- Enright (*Journal of Animal Science* **71** (9) 2395-405, 1993) discloses that thyrotropin releasing hormone was ineffective in eliciting GH release

- Robberecht (*Neuroendocrinology* **56** (4) 550-60, 1992, entitled "Angiotensin II is retained in gonadotrophs of pituitary cell aggregates cultured in serum-free medium but does not mimic the effects of exogenous angiotensins and luteinizing-hormone-releasing hormone on growth hormone release") discloses that LHRH has both inhibitory and stimulatory effects on GH release in cultured pituitary cell aggregates.

The foregoing references support the following conclusions: (a) one cannot "predict" whether, or the extent to which, a given compound will activate a receptor, or antagonize it; (b) even if one can show that receptor activation or antagonism occurs in vitro, such a result is not necessarily predictive of what will happen *in vivo*. Accordingly, "undue experimentation" would be required to determine whether, or under what conditions, the compounds of claim 4 will antagonize CRF receptors. It may be the case that the compounds of claim 4 have been disclosed in the prior art; perhaps they have been claimed in a U.S. Patent. But the fact that a given compound has been

disclosed does not mean that it is enabled. Even the fact that a claim in a U.S. Patent is drawn to a given compound does not mean that evidence of enablement has been provided in that patent (notwithstanding the presumption of validity that is conferred upon all U.S. patents). Accordingly, to overcome this ground of rejection, more will be required than just a showing that someone else has disclosed the compounds.

Consider next the issue of GH secretagogues. It is acknowledged that there do exist compounds which are effective to promote release of GH *in vivo*. However, there is no evidence that the compounds recited in claims 16 and 18 are in fact effective to promote release of GH in vitro or *in vivo*. Again, the compounds of claims 16 and 18 may have been previously disclosed, but this does not constitute evidence of enablement.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Accordingly, "undue experimentation" would be required to determine which of the compounds will be effective to antagonize CRF receptors, or to determine which of the

compounds of claims 16 or 18 will promote release of GH.

Another matter concerns the term "pharmaceutical" (e.g., claim 4). In the event that applicants should choose, for one reason or another, to amend the claims so that growth hormone *per se* is not recited (as opposed to growth hormone *secretagogue*), the claims will be rejected for lack of enablement because of the term "pharmaceutical". This term carries with it the implied assertion of therapeutic efficacy, which is not in evidence. First, as indicated, there is no evidence that the compounds which are asserted (in claim 4) to be CRFA's do in fact antagonize CRF receptors. But even if evidence of *in vitro* binding were to be provided, this would not amount to evidence of therapeutic efficacy. As for GHS's, it may be the case that some GHS's are therapeutically effective for one purpose or another, but the fact is that only a small portion of those compounds that are effective to promote release of GH in vitro are actually effective to treat a disease in a mammal. The reasons include issues of degree or extent of GH release, pharmacokinetics, and survivability of the asserted GHS *in vivo*. Another issue concerns the degree of criticality of the GH deficiency. Many diseases cannot be successfully treated regardless of how much GH (or secretagogue) may be administered.

Accordingly, it is suggested that applicants provide evidence that the compounds of claims 4, 16 and 18 can be used as asserted, and that the term "pharmaceutical" be deleted

at every occurrence.

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Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 4, the following is recited:

"n and w are 0, 1 or 2 provided that n and w cannot both be **O** at the same time"

Here, it appears that the letter "O" has been used, rather than the number "0".

✧

The following is a quotation of 35 USC 103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Carpino (USP 6,107,306) in view of Chen (USP 6,432,989).

Carpino discloses treatment of sleep disorders using GHS's; also disclosed (col 64, line 12) is "ES-2". Carpino does not suggest combining a GHS with a CRFA.

Chen discloses treatment of sleep disorders; also disclosed (col 27, line 36) is "ES-1". Chen does not suggest combining a GHS with a CRFA..

Thus, a medical practitioner of ordinary skill would have been motivated to combine the CRFA of Chen with the GHS of Carpino to obtain additive effects. The claims are rendered obvious.

✧

Claims 4, 13, 14, 16, 18-22, 30, 31, 33 are rejected under 35 U.S.C. §103 as being unpatentable over Carpino (USP 6,107,306) in view of Chen (USP 5,962,479).

Carpino discloses treatment of Alzheimer's Disease using GHS's; also disclosed (col 64, line 12) is "ES-2". Carpino does not suggest combining a GHS with a CRFA.

Chen discloses treatment of Alzheimer's Disease; also disclosed (col 55, line 34) is "ES-1". Chen does not suggest combining a GHS with a CRFA..

Thus, a medical practitioner of ordinary skill would have been motivated to combine the CRFA of Chen with the GHS of Carpino to obtain additive effects. The claims are

rendered obvious.

✧

- The reference Black (Scientific American, 1995) was stricken from the IDS because it was not received, and moreover, the citation may erroneous.

- Those references published in a foreign language (e.g., WO 98/29397) were stricken from the IDS because of the absence of a translation.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.